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(54) Title: PHARMACEUTICAL COMPOSITIONS

(57) Abstract

The invention provides products containing tumour necrosis factor (TNF), and taurolidine and/or taurultam as a combined preparation for simultaneous, separate or sequential use for treatment of patients suffering from medical conditions mediated by TNF.

FOR THE PURPOSES OF INFORMATION ONLY

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PHARMACEUTICAL COMPOSITIONS

This invention relates to pharmaceutical compositions containing Tumour Necrosis Factor (TNF) and to compositions of use in medicine for combating the effects of Tumour Necrosis Factor.

Tumour Necrosis Factor was discovered by Carswell et al in 1975 (Proc. Nat. Acad. Sci. USA, 1975:72, c666-70) as a soluble factor released by the host after exposure to bacterial endotoxins and being responsible for tumour cytotoxicity. TNF has been shown to be a protein consisting of 157 amino acids. It has an apparent molecular weight of 17,350 by SDS-PAGE and of 45,000 gel filtration. Recombinant human TNF protein is now available in relatively large quantities. When the amino acid sequence of the molecule was determined, it was found that there are slightly differing forms of TNF and that TNF-alpha was identical to cachectin, a macrophage product believed to cause adverse host responses to bacterial invasion, including the wasting condition cachexia, and observed in the serum of tumour bearing animals.

TNF has been shown to have a wide range of biological activities in vitro. In addition to its antitumour effects, TNF is involved in immunoregulation, metabolism, haematopoiesis and musculoskeletal growth. Thus, TNF has been shown to lyse certain tumour cells, augment normal diploid fibroblast cell growth, induce differentiation of leukemic cells, inhibit certain haematopoietic progenitor cell growth, induce production of granulocyte-macrophage colony stimulating factor, modify structure and function of vascular endothelium, activate neutrophils and eosinophils, activate monocytes with resultant stimulation of IL-1 and prostaglandin E2 secretion, upregulate fibroblast

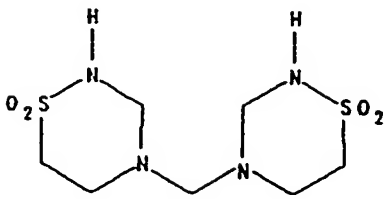
expression of Class 1 MHC antigens, stimulate the production of prostaglandin E2 and collagenase in fibroblast and synovial cells, induce bone and cartilage resorption, inhibit proteoglycan synthesis, suppress lipoprotein lipase synthesis in adipocytes and prevent differentiation of preadipocytes to adipocytes. Recently, TNF has been reported as playing a role in the progression of AIDS related complex (ARC) to AIDS itself.

There is thus a wide range of medical conditions in which administration of TNF is indicated. However, TNF is very toxic. It appears to be responsible for many or all of the symptoms of endotoxaemia caused by lipopolysaccharide (LPS). Such toxicity clearly represents a serious problem in using TNF in therapy. Thus, in attempts to evaluate TNF in the treatment of cancer, clinical trials have shown that fever, chills, fatigue and headache were commonly observed. Inflammation was also observed at the injection site. Anaemia and hyperglycaemia have also been observed in test animals. Tests for the presence of antibodies to TNF have so far been uniformly negative.

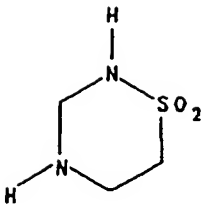
We have found that the antibacterial compounds taurolidine and taurultam are significantly effective in reducing the toxicity and side effects of TNF. While we do not wish to be bound by theoretical considerations, it appears possible that taurolidine and taurultam interfere with synergism between TNF and endotoxins or metabolic products derived from endotoxins. This is supported by the finding that taurolidine and taurultam do not inhibit the antitumour effect of TNF but, in fact, augment such cytotoxicity. We have further found that taurolidine and taurultam do not have a significant cytotoxic effect against normal cells and may thus be safely used in combination with TNF in combating tumours.

Taurolidine and taurultam are closely related and

have the formulae set out below:



TAUROLIDINE



TAURULTAM

Both the above compounds are methylol tranfer agents. Taurolidine can tranfer three methylol groups to leave as a residue the very well tolerated compound taurinamide. Taurultam is, in fact, produced during the methylol transfer process of taurolidine, itself being capable of transferring a single methylol group to leave a residue of taurinamide. Thus, the two compounds are essentially equivalent.

As indicated above, the primary effect of taurolidine and taurultam is in reducing or eliminating the toxic side effects of TNF. Consequently, such combined therapy will also be beneficial in all of the other medical indications of TNF, in each of which the toxicity of TNF represents a negative indication. Taurolidine and/or taurultam do not need to be administered simultaneously with TNF or in the same composition although compositions containing both components are convenient.

According to one aspect of the invention we provide a method of treatment of medical conditions mediated by TNF wherein a patient suffering from one or more of such conditions is treated with effective amounts of TNF and of taurolidine and/or taurultam.

The invention also includes products containing tumour necrosis factor (TNF), and taurolidine and/or taurultam as a combined preparation for simultaneous,

separate or sequential use for treatment of patients suffering from medical conditions mediated by TNF.

Thus the invention also provides a process of manufacturing a pharmacautical composition, wherein TNF is admixed with taurolidine and/or taurultam.

The invention further provides a use of taurolidine and/or taurultam to reduce the toxic side effects of TNF in the human or non-human animal body.

It is believed that other agents known to be involved in tumour metabolism may also advantageously be co-administered in conjunction with the above combined therapy. Such agents include gamma-interferon, interleukin-1 and interleukin-2. Cytotoxic agents such as adriamycin and actinomycin D may also be co-administered.

The active compounds here concerned will normally be administered by the parenteral route, for example intravenously. The compositions may thus comprise water for injection together with saline and other injectable components. The water-solubility of taurolidine is rather low and it may be advantageous to include one or more substances increasing the solubility of taurolidine and to a lesser extent taurultam, for example a polyol such as glucose. Such compositions are described in European Patent Application 253662.

TNF will be administered in accordance with the invention in the dose range 1 ng/kg to 100 ng/kg units such as ampoules for injection, will normally contain 1 ng to 100 ng, of TNF.

Taurolidine and/or taurultam will be administered at significantly higher doses, namely 150 mg/kg to 450 mg/kg per day, preferably 300 mg/kg to 450 mg/kg per day. Relatively large volumes of aqueous solutions containing taurolidine and/or taurultam will thus be administered containing, for example, 10 g to 30 g of taurolidine and/or taurultam. It may be convenient to

administer these compounds by infusion in view of the relatively large volumes concerned, conveniently at intervals throughout the day.

As indicated above, TNF is believed to be the principle mediator of the adverse effects produced by bacterial sepsis. In view of the beneficial effect of taurolidine and taurultam in reducing the toxic effects of TNF, it is also beneficial to administer these compounds in any medical condition where TNF is active adversely. Taurolidine and/or taurultam can thus be advantageously administered in the treatment of sepsis. The half life of TNF in the vascular system is relatively short, for example 90-180 minutes. In sepsis, it appears to be liberated as a single major pulse. Consequently, taurolidine and/or taurultam are preferably administered prophylactically in conditions where septic shock and/or endotoxaemia are likely to occur.

However, there are certain conditions, notably obstructive jaundice, where TNF levels in the blood remain massively high. Similarly, where tumours produce TNF, resulting in many of the symptoms associated with endotoxaemia, administration of taurolidine and/or taurultam will be beneficial in alleviating such symptoms. The invention thus extends to the therapeutic administration of taurolidine and/or taurultam to patients suffering from tumours or other conditions in which TNF is chronically present in detectable amounts in the blood.

The following non-limiting Examples are provided to illustrate further the invention:

Example 1 - Solution

Bis-(1,1-dioxo-perhydro-1,2,4-thiadiazin-4-yl)-methane (taurolidine)	400g
Polyvinylpyrrolidone (Kollidone 17)	1000g
Sterile water to	20 litres

15 Litres double distilled pyrogen free water are filled into a 25 litre glass vessel with stirrer and intensive reflux device and heated to 50°C with stirring. The taurolidine (400 g) is added followed by PVP (Kollidone 17; 1000 g). After dissolution, the solution is cooled and the pH adjusted to 6.0 with a few drops of 0.1 N hydrochloric acid. The solution is then passed through an absorption filter to remove microorganisms and pyrogens and through a sterilising millipore filter before being filled into 100 ml vials which are finally autoclaved.

Example 2 - Solution

Taurultam	990g
Sterile water ad	22 litres

The taurultam is dissolved in the sterile water and filled into sterile bottles, 250ml in each.

Example 3 - Tablet

Taurolidine	550g
Amylum maydis	60g
Kollidone 25 (polyvinylpyrrolidone)	50g
Plasdon XL	20g
Magnesium stearate	6g
Distilled water	200g

1000 tablets, each containing 500 mg taurolidine, are produced by conventional means using the above formulation.

In an alternative tablet formulation, the amylum maydis is replaced by 60g amylum orizae.

Example 4 - Solution

Taurolidine		440g
Pharmaceutical gelatin		88g
Sodium chloride		99g
Sterile water	to	22 litres

The components are dissolved in the sterile water, if necessary using gentle warming and sonication. The solution is then filled into sterile bottles, 500 ml in each.

Claims

1. Products containing tumour necrosis factor (TNF), and taurolidine and/or taurultam as a combined preparation for simultaneous, separate or sequential use for treatment of patients suffering from medical conditions mediated by TNF.

2. A product as claimed in claim 1, wherein said TNF and taurolidine and/or taurultam can be administered sequentially.

3. A method of treatment of medical conditions mediated by TNF wherein a patient suffering from one or more said conditions is treated with effective amounts of TNF and of taurolidine and/or taurultam.

4. A method of treatment as claimed in claim 3, wherein said effective amounts of TNF and of taurolidine and/or taurultam are co-administered.

5. A pharmaceutical composition comprising taurolidine and/or taurultam and TNF.

6. A process of manufacturing a pharmaceutical composition, wherein TNF is admixed with taurolidine and/or taurultam.

7. Use of taurolidine and/or taurultam to reduce the toxic side effects of TNF in the human or non-human animal body.

8. A method of treatment of tumours or other conditions in which tumour necrosis factor (TNF) is chronically present in detectable amounts in the blood wherein an effective amount of taurolidine and/or taurultam is administered to a patient suffering from

one or more of said conditions.

9. Use as claimed in claim 8, wherein a tumour or obstructive jaundice causes production of said TNF.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/00524

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: A 61 K 37/02, A 61 K 31/54 / (A 61 K 37/02, 31:54)

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	WO, A, 8802632 (PRESIDENT AND FELLOWS OF HARVARD COLLEGE) 21 April 1988 see page 5; abstract ---	1,2,5-7
A	Chemical Abstracts, volume 106, no. 7, 16 February 1987, (Columbus, OH, US), M.K. Browne et al.: "Studies on the antiendotoxin properties of taurolin in animals and man", see page 20, abstract 43490j, & Recent Adv. Chemother, Proc. Int. Congr. Chemother., 14th, 1985, (Antimicrobial Sect. 3), 2075-6 ---	1,2,5-7
A	Chemical Abstracts, volume 103, no. 25, 23 December 1985, (Columbus, OH, US), P.G. Waser et al.: "Pharmacology and toxicology of taurolidine", see page 34, abstract 205594p, & Taurolin, 1985, 24-37 --- ./.	1,2,5-7

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
21st June 1991	29.08.91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	F.W. HECK

International Application No PCT/EP 91/00524

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	Chemical Abstracts, volume 94, no. 23, 8 June 1981, (Columbus, OH, US), E. Myers et al.: "The interaction between taurolin and endotoxin", see page 53, abstract 185696p, & Microbios Lett., 1980, 13(51-52), 141-7	1,2,5-7

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers 3,4,8,9 because they relate to subject matter not required to be searched by this Authority, namely:
see PCT Rule 39.1(iv)

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9100524 SA 45750

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/08/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A- 8802632	21-04-88	EP-A-	0287633	26-10-88
		JP-T-	1500905	30-03-89
		US-A-	4980160	25-12-90